In response to the Notice of Draftsperson's Patent Drawing Review, Applicants enclose herewith new corrected drawings. As requested by the Examiner, Applicants have amended the specification to include a proper priority claim.

Applicants acknowledge with gratitude the Examiner's consideration of references cited in their Information Disclosure Statements filed on December 17, 1999 and December 4, 2000. Applicants agree that consideration of reference CJ on page 3 of the IDS filed on December 17, 1999 is unnecessary in view of the Examiner's consideration of the full PCT document (WO 97/08190).

The Examiner's objection to claim 53 is moot in view of the cancellation of claims 51-53. The remaining rejections are separately addressed below.

1. ***Claims 16-22, as amended, satisfy the requirements of 35 U.S.C. § 112, second paragraph***

Claims 16-22 and 51-53 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. The rejection of claims 51-53 is moot in view of the cancellation of those claims. The rejection of claims 16-22 is addressed by amendment in part and is traversed in part.

At page 6, the Office Action states that the phrase "at least about" is unclear as to the lower limit, and that the rejection would be overcome by deleting the word "about." Applicants respectfully traverse the rejection and respectfully submit that the term "at least about" satisfies the requirements under § 112, second paragraph. The term "at least about" is conventionally used in the art, as evidenced by the description in WO 95/19359, i.e., the prior art cited in the Office Action as the basis for the § 102 rejection. *See* WO 95/19359 at page 38, lines 28-29 ("[E]ach library contains *at least about* 100 different compounds"); and page 39, lines 1-3 ("[T]he library contains *at least about* 100 different members...."). *See also* MPEP 2173.05. Applicants respectfully request that the rejection of the phrase "at least about" be withdrawn.

At page 6, the Office Action states that it is unclear whether the claimed screening method is intended to include the "production" steps used to define the mass-

coded combinatorial library. Applicants have amended claim 16 to delete production limitations from the preamble of the claim. Instead, the relevant structural features of the mass-coded library are now recited in step (a) of the claim. Support for this amendment can be found throughout the specification and in original claim 16.

Applicants submit that it is clear that "production" steps are not included as required steps in the method claimed in amended claim 16. Accordingly, Applicants respectfully request that this ground for rejection be reconsidered and withdrawn.

In view of the foregoing, Applicants respectfully request that the rejection of claims 16-22 under 35 U.S.C. § 112, second paragraph, be reconsidered and withdrawn.

2. ***Claims 16-19 and 22, as amended, are not anticipated by Rebek et al.***

Claims 16-19, 22, and 51-53 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Rebek *et al.*, WO 95/19359. The rejection of claims 51-53 is moot in view of the cancellation of those claims. Applicants respectfully traverse the rejection as applied to amended claims 16-19 and 22.

Claim 16 is directed to a method for identifying a ligand for a biomolecule, comprising contacting the biomolecule with a mass-coded combinatorial library, separating biomolecule-ligand complexes from unbound members of the library, dissociating the biomolecule-ligand complexes, and determining the molecular mass of each ligand. The mass-coded combinatorial library comprises compounds of the general formula XY_n, wherein n is an integer from 2 to about 6, X is a scaffold, and each Y is, independently, a peripheral moiety. There exist at least 250 distinct combinations of n peripheral moieties in the compounds of the library, and each of at least 90% of the combinations of n peripheral moieties has a molecular mass sum that is distinct from all other combinations of n peripheral moieties in the library. Because mass redundancy in the library is controlled, it is possible to determine, by mass alone, the combination of n peripheral moieties present in a member of the mass-coded library that is found to bind to the biomolecule of interest.

Rebek *et al.* teaches a process for making combinatorial libraries comprising compounds of the general formula XY_n. Rebek *et al.* further teaches a methods for screening the libraries to identify molecules that bind to a ligate (*e.g.*, an antibody, receptor, enzyme, or microbe). However, despite the Examiner's statements to the contrary, Rebek *et al.* does not teach a mass-coded combinatorial library. Indeed, Rebek *et al.* discloses no efforts at all to control mass redundancy (*i.e.*, the number of library members with the same molecular mass). One of ordinary skill in the art would readily appreciate that the degree of mass redundancy will increase with increasing size of a combinatorial library, unless methods are found to control mass redundancy. It is just this problem that Applicants have solved.

Rebek *et al.* discloses at page 70 that the structures of the library molecules of interest are ideally deduced from their molecular weights. However, Rebek *et al.* readily recognizes that, in the libraries it describes, the structure of a library molecule may not be uniquely determined by its molecular weight. Indeed, Rebek *et al.* provides no working example of a screening procedure that relies upon mass spectroscopy to identify active library members. Instead, in Example 11, at pages 74-83, Rebek *et al.* describes an iterative screening procedure to identify trypsin inhibitors. According to this approach, a series of sub-libraries was constructed to progressively narrow down the library components contributing to activity. Only in this way was it possible to determine which member of the original library was active in the trypsin assay. Applicants' invention renders such iterative procedures unnecessary, even for very large libraries.

Rebek *et al.* does not anticipate amended claim 16, because Rebek *et al.* fails to teach a mass-coded library, as recited in the claim. Claims 17-19 and 22 each depend from and incorporate all of the limitations of independent claim 16. Thus, claims 17-19 and 22 are not anticipated by Rebek *et al.* for the same reasons discussed above for independent claim 16. Accordingly, Applicants respectfully request that the rejection of claims 16-19 and 22 under 35 U.S.C. § 102(b) be reconsidered and withdrawn.

3. Claims 16-22, as amended, are nonobvious over Rebek et al. in view of Hsieh et al.

Claims 16-20, 22 and 51-53 stand rejected under 35 U.S.C. § 103 as unpatentable over Rebek *et al.*, in view of Hsieh *et al.*, *Molec. Diversity* 2:189-196 (1996). The rejection of claims 51-53 is moot in view of the cancellation of those claims. Applicants respectfully traverse the rejection as applied to amended claims 16-20 and 22.

As discussed above, Rebek *et al.* fails to disclose a mass-coded combinatorial library.

4. Claims 16-19 and 21-22, as amended, are nonobvious over Rebek et al. in view of Breeman et al.

Claims 16-19, 21-22, and 51-53 stand rejected as being unpatentable over Rebek *et al.*, in view of Breeman *et al.*, *Anal. Chem.* (1997). The rejection of claims 51-53 is moot in view of the cancellation of those claims. Applicants respectfully traverse the rejection as applied to amended claims 16-19 and 21-22.

CONCLUSIONS

In view of the amendments and arguments set forth above, Applicants submit that each of the rejections contained in the Office Action mailed on November 2, 2001 has been addressed and overcome, and that the claims are in condition for early allowance. Claims 54-63 depend on claim 16 and therefore are allowable for the reasons discussed above for claim 16. If the Examiner believes that any further discussion of this communication would be helpful, he is invited to contact the undersigned at the telephone number provided below.

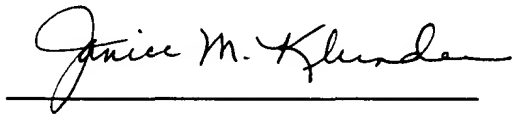
Applicants enclose a Petition for a Two-Month Extension of Time pursuant to 37 C.F.R. § 1.136, up to and including April 2, 2002, to respond to the Examiner's Action mailed on November 2, 2001.

No other fees are believed to be due in connection with this response. However, pursuant to 37 C.F.R. § 1.136(a)(3), the Examiner is authorized to charge any fee under

37 C.F.R. § 1.17 applicable in the instant, as well as in future communications, to Deposit Account No. 08-0219. Such an authorization should be treated as a constructive petition for extension of time in the concurrent as well as future communications in the above-identified application.

Please also charge any payments due or credit any overpayments associated with this matter to our Deposit Account No. 08-0219.

Respectfully submitted,



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Appendix A

16. (*Thrice Amended*) A method for identifying a member of a mass-coded combinatorial library which is a ligand for a first biomolecule, the method comprising the steps:

(a) contacting the first biomolecule with a mass-coded combinatorial library, said mass-coded combinatorial library comprising compounds of the general formula XY_n, wherein n is an integer from 2 to about 6, X is a scaffold and each Y is, independently, a peripheral moiety, wherein there exist at least about 250 distinct combinations of n peripheral moieties, and wherein each of at least about 90% of the combinations of n peripheral moieties has a molecular mass sum that is distinct from the molecular mass sum of all other combinations of n peripheral moieties, whereby members of the mass-coded combinatorial library which are ligands for the biomolecule bind to the first biomolecule to form first biomolecule-ligand complexes and members of the mass-coded library which are not ligands for the first biomolecule remain unbound;

(b) separating the first biomolecule-ligand complexes from the unbound members of the mass-coded combinatorial library;

(c) dissociating the first biomolecule-ligand complexes; and

(d) determining the molecular mass of each ligand to identify the set of n peripheral moieties present in each ligand;

wherein the molecular mass of each ligand corresponds to a set of n peripheral moieties present in that ligand, thereby identifying a member of the mass-coded combinatorial library which is a ligand for the first biomolecule.

17. The method of claim 16 wherein the biomolecule is immobilized on a solid support.

18. The method of claim 17 wherein the solid support is a water-insoluble matrix contained within a chromatographic column.

19. The method of claim 16 wherein a solution comprising the biomolecule is contacted with the mass-coded combinatorial library to form, if one or more members of the combinatorial library are ligands for the biomolecule, a solution comprising biomolecule-ligand complexes and unbound members of the mass-coded combinatorial library.

20. The method of claim 19 wherein the unbound members of the mass-coded combinatorial library are separated from the biomolecule-ligand complexes by directing the solution comprising biomolecule-ligand complexes and the unbound members of the mass-coded combinatorial library through a size exclusion chromatography column, whereby the unbound members of the mass-coded combinatorial library elute from said column after the biomolecule-ligand complexes.

21. The method of claim 19 wherein the unbound members of the mass-coded combinatorial library are separated from the biomolecule-ligand complexes by contacting the solution comprising biomolecule-ligand complexes and the unbound members of the mass-coded combinatorial library with a size-exclusion membrane, whereby the unbound compounds pass through said membrane and the biomolecule-ligand complexes do not pass through said membrane.

22. The method of claim 16 wherein the biomolecule is a protein or a nucleic acid molecule.

54. The method of claim 16, further comprising the steps:

(e) contacting a second biomolecule with the mass-coded combinatorial library, whereby members of the mass-coded combinatorial

library which are ligands for the second biomolecule bind to the second biomolecule to form second biomolecule-ligand complexes;

(f) separating the second biomolecule-ligand complexes from the unbound members of the mass-coded combinatorial library;

(g) dissociating the second biomolecule-ligand complexes;

(h) determining the molecular mass of each ligand for the second biomolecule; and

(i) determining which molecular mass or masses determined in step (d) are not determined in step (h), thereby providing the molecular masses of members of the mass-coded combinatorial library which are ligands for the first biomolecule but are not ligands for the second biomolecule;

wherein each molecular mass determined in step (i) corresponds to a set of n peripheral moieties present in a ligand for the first biomolecule which is not a ligand for the second biomolecule, thereby identifying a member of the mass-coded combinatorial library which are ligands for the first biomolecule but are not ligands for the second biomolecule.

55. The method of claim 54 wherein the first biomolecule and the second biomolecule are each, independently, a protein or a nucleic acid molecule.

56. The method of claim 55 wherein the first biomolecule and the second biomolecule are each a protein, and the amino acid sequence of the second biomolecule is derived from the amino acid sequence of the first biomolecule by insertion, deletion or substitution of one or more amino acid residues.

57. The method of claim 55 wherein the first biomolecule is a first protein and the second biomolecule is a second protein, said first and second proteins having the same amino acid sequence, wherein said first and second proteins have different posttranslational modifications.

58. The method of claim 57 wherein the first protein differs from the second protein in extent of phosphorylation, glycosylation or ubiquitination.

59. The method of claim 55 wherein the second biomolecule is a complex of the first biomolecule with a ligand.

60. The method of claim 55 wherein the first biomolecule and the second biomolecule are each immobilized on a solid support.

61. The method of claim 60 wherein the solid support is a water-insoluble matrix contained within a chromatographic column.

62. The method of claim 55, wherein one or both of steps (b) and (f) is performed by contacting a solution comprising first biomolecule-ligand complexes or second biomolecule-ligand complexes and unbound members of the mass-coded combinatorial library with a size exclusion chromatography column, whereby the unbound members of the mass-coded combinatorial library elute from the column after the first biomolecule-ligand complexes or the second biomolecule-ligand complexes.

63. The method of claim 55, wherein one or both of steps (b) and (f) is performed by contacting a solution comprising first biomolecule-ligand complexes or second biomolecule-ligand complexes and unbound members of the mass-coded combinatorial library with a size exclusion membrane, whereby the members of the mass-coded combinatorial library pass through said membrane and the first biomolecule-ligand complexes or second biomolecule-ligand complexes do not pass through said membrane.

Appendix B

In the Specification:

At page 1, lines 4-7:

This application is a divisional of U.S. Patent Application Serial No. 09/024,592, filed on February 17, 1998, now U.S. Patent No. 6,207,861, which claims the benefit of U.S. Provisional Application No. 60/070,456, filed January 5, 1998, the contents of which are incorporated herein by reference in their entirety.

In the Claims:

16. (*Thrice Amended*) A method for identifying a member of a mass-coded combinatorial library which is a ligand for a first biomolecule, ~~said mass-coded combinatorial library comprising compounds of the general formula XY_n, wherein n is an integer from 2 to about 6, X is a scaffold and each Y is, independently, a peripheral moiety, wherein said mass-coded combinatorial library is produced by reacting a scaffold precursor having n reactive groups, wherein each reactive group is capable of reacting with at least one peripheral moiety precursor to form a covalent bond, with a peripheral moiety precursor subset selected from a peripheral moiety precursor set, said peripheral moiety precursor subset comprising a sufficient number of distinct peripheral moiety precursors such that there exist at least about 250 distinct combinations of n peripheral moieties derived from said peripheral moiety precursors,~~ said method comprising the steps of:

(a) contacting the first biomolecule with the mass-coded combinatorial library, said mass-coded combinatorial library comprising compounds of the general formula XY_n, wherein n is an integer from 2 to about 6, X is a scaffold and each Y is, independently, a peripheral moiety, wherein there exist at least about 250 distinct combinations of n peripheral moieties, and wherein each of at least about 90% of the combinations of n peripheral moieties has a molecular mass

sum that is distinct from the molecular mass sum of all other combinations of n peripheral moieties, whereby members of the mass-coded combinatorial library which are ligands for the biomolecule bind to the first biomolecule to form first biomolecule-ligand complexes and members of the mass-coded library which are not ligands for the first biomolecule remain unbound;

(b) separating the first biomolecule-ligand complexes from the unbound members of the mass-coded combinatorial library;

(c) dissociating the first biomolecule-ligand complexes; and

(d) determining the molecular mass of each ligand to identify the set of n peripheral moieties present in each ligand;

wherein the molecular mass of each ligand corresponds to a set of n peripheral moieties present in that ligand, thereby identifying a member of the mass-coded combinatorial library which is a ligand for the first biomolecule.